UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,449	08/25/2003	Manne Satyanarayana Reddy	BULK 3.0-026	1649

45776 7590 11/30/2006

DR. REDDY'S LABORATORIES, INC.
200 SOMERSET CORPORATE BLVD
SEVENTH FLOOR,
BRIDGEWATER, NJ 08807-2862

EXAMINER	
CHANG, CELIA C	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/647,449
Filing Date: August 25, 2003
Appellant(s): REDDY ET AL.

Robert. A. Franks
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 6, 2006 appealing from the Office action mailed March 6, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is mostly correct. However, the rejection of ground A. should include claim 39 as well, see inclusion in office action dated March. 6, 2006.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Evidence applied in rejection

5,132,924 Grell et al. 5-1995

*Grell et al. "Repaglinide and related hypoglycemic benzoic acid derivatives" J. Med. Chem. v.41, p.5219-5246 (2998)
*Brittain "Polymorphism in pharmaceutical solids" Marcel Dekker, p. 2, 178-179, 185, 219 (1999)
*Rouli "The right stuff" Chem. Eng. New. p.32-35 (2003)

*US Pharmacopia #23, national formulary #18 p.1843-1844 (1995)

State-of-the-art evidence rebutting appellants' argument

* EXHIBIT A comparison of IR

5,672,612 Ronsen et al. 9-1997

*Berstein "Polymorphism in molecular crystals" p. 253-254, 272-273 (2002)

*Davidovich et al. "Detection of polymorphism....." Am. Phar. Rev. v.7(1) pages 10, 12, 14, 16, 100 (2004)

*Polymorphism Wikipedia, encyclopedia on internet (2006)

*Baumann et al. "Reactions with microorganism....." Helvetica Chimica Acta 41, p.2362-79 (1958) with English abstract.

*Muzafffar et al. "Polymorphism and drug availability" J. Phar. 1(1) p.59-66 (1979)

*Jain et al. "Polymorphism in pharmacy" Indian Drugs 23(6) p. 315-329 (1986)

*Otsuka et al. "Effect of polymorphic forms....." Chem. Pharm. Bull. 47(6) p.852-856 (1999)

*Doelker "Thematic session. Cyrstalline modification....." Ann. Phar. Fr. 60:161-176 (2002) and English translation p.1-36.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims. The rejections are found in the office actions dated July 15, 2005 and Mar. 6, 2006 and hereby recited:

(A) The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 38-39, 40-49 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,3,12,924 (recited on 1449).

See col. 89-90 the non-crystalline "residue" after vacuo of solvent ethanol. Noncrystalline solid is amorphous and the process is the same as the claimed (see col. 89-90, example 12) i.e. dissolving compound in ethanol, evaporating the solvent to separate the residue. (An inadvertent error was made in citing the location of the prior art and the error is hereby corrected. However, Appellants had no problem in locating the correct information as evidenced by the recitation in the brief on p.6).

Please note that it is well known in the art that there is only one amorphous product of a given material. (see Ulicky comprehensive dictionary of physical chemistry, p. 21, it was disclosed that solid can be subdivided into crystalline or amorphous. See concise encyclopedia chemistry, where it was defined that multiple crystalline forms are called polymorphs). Any x-ray diffraction of an amorphous material is only to show no diffraction or non-crystalline. Therefore, the incorporation of x-ray diffraction into the base claim does not change the product and anticipation is found.

(B) The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 34-35 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,132,924.

See col. 16, Figure 4 crystallized compound of the claims, form A, solid, and col. 33, form A is the low melting point form of the compound. Please note that one category of patentable invention is a "product". A novel or unobvious chemical product is identified first by its "chemical nature, i.e. elemental content and their ratios, i.e. the chemical identity. It was a well known "fact" that "many pharmaceutical solids exhibit polymorphism which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Thus *in the strictest sense, polymorphs are different crystalline forms of the* ***same pure substance*** *in which the molecules have different arrangements and/or different conformations of the molecules* (see Brittain p. 1-2). The term form III does not offer any demarcation of the product from the prior art crystalline product as represented by the compound name since form III or form A, B or C in the prior art are not notation known in the chemical art representing conventional characteristic in demarcating chemical products.

. Please note that, the finding of anticipation is whether the claims and the prior art are "same identical" product not what physical parameters are used in claiming them. In so far as the instant claims are concern, to the extend the identifier being IR, the instant product and the prior art products are essentially the same i.e. compare figure 3 of the instant application and combined part I and II of figure 4 of US 5,132,924, thus, same product. Although 2 theta values and d-spacing are useful in identifying different crystalline forms, margin of error existed (see page 16, specification). Therefore, the single 2 theta pattern does not demarcate any product from another without multiple identifiers which when compared two forms clearly can demarcate each to be different products given margin in error.

(C) The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-37, 39, 50-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grell et al. US 5,312,924 in view of Grell et al. j. Med. Chem (recited on 1449) and Brittain.

Determination of the scope and content of the prior art (MPEP §2141.01)

Grell et al. '942 disclosed compound that anticipated the base claims which was pointed out supra.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the Grell et al. disclosure and the instant dependent claims is that the physical property of the prior art product was not expressly included, or the process of making the products employed alternative solvents. Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are operable (see page 5227 paragraph below table 2). Brittain taught that "*in the strictest sense, polymorphs are different crystalline forms of the* ***same pure substance*** *in which the molecules have different arrangements and/or different conformations of the molecules* (see Brittain p. 1-2).

Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art would find the claims prima facie obvious because the instant claims differ from the known product merely by forms and the physical properties innate to the forms. As it was recognized in the art that in the pharmaceutical field, many solids exhibit polymorphism which is the innate nature of the particular drug (see US Pharmacopia #23, national formulary #18). There is nothing unobvious about the innate nature of a drug. It is also recognized in the art that the innately existing different "morph" will display different physical properties such as X-ray diffraction pattern, melting point etc. (see Brittain p. 178-179, 219). Just because it is "different" does not merit the new form patentability. As it was clearly stated by one having ordinary skill in the art in Brittain (p. 1-2) supra, as well as set forth by the court in In re Cofer 148 USPQ 268. Ex parte Hartop 139 USPQ 525, that products which are merely different forms of known compounds, notwithstanding that some desirable results are obtained

therefrom, are unpatentable. The instant specification and claims disclosed known compound S-repaglinide form III, which is the ***same pure substance*** as the prior art, only *has different arrangements and/or different conformations of the molecule*. Mere difference in physical property is well known conventional variation for the same pure substance (see Brittain p.1-2), i.e. prima facie obvious. For a known compound with defined chemical nature to be patentable for a new form, it must have a patentability basis of an advantage in terms of stability, formulation, solubility, bioavailability, easy of purification, preparation or synthesis, hydroscopicity, recovery or prevention of precipitation etc. (see p. 185).

The employment of different solvents in the crystallization process are art recognized conventional variation for obtaining different forms (see Grell J. Med. Chem p.5227). In absent of unexpected result it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product (please note that channel or associated solvates/hydrates are identical crystalline form with different physical properties because of the existence of solvents/water).

Even if the product of the instant application and the prior art differ in X-ray diffraction or "form" the mere difference in physical parameter such as X-ray diffraction pattern does not offer any unexpected advantage of prior art product with the same chemical property and biological property i.e. a mere variation in physical property which flows naturally with the changing form.

(D) Claims 8-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The analysis is applied to the instant case.

Nature of invention

Claims 8-18 are drawn to pharmaceutical composition comprising (S)-repaglinide as a solid wherein at least 80% by weight of said solid (S)-repaglinide is in *crystalline form III*.

The state of the art and predictability

The pharmaceutical formulation field is well aware that polymorphs when being formulated into compositions may undergo transformation thus, the particular form may not be the same form after processing, compressing etc. (see Rouhi Chem. Eng. New, see p. 34-35). Therefore, in absence of any description or factual evidence, how a crystalline form can be maintained in a composition to minimize transformation, no assumption can be made that the meta-stable polymorph will be maintained upon compression, tableting etc.

The amount of guidance and working examples

The specification lacks description and enablement that the pharmaceutical composition contains the claimed "form" without transformation. There is no factual basis provided in the specification as to support the transformation of less than 1-5% as found in claims 9-14. No description nor enabling support can be found as to how such limited transformation can be operable, i.e. temperature, pressure, carrier, etc.

In an article provided by applicants *tricky business*, it was evidenced that maintaining crystals in its desirable form is a tremendous effort. In the instant application, no example was found as to how a value of 80% form III was arrived in any solid composition; nor was any processing resulted in a composition comprising (S)-repaglinide as a solid wherein at least 80% by weight of said solid is in crystalline form III. Please note that, the transformation of any amount of the form III to other forms indicated the metastable nature of Form III. Therefore, absent of *any description or enablement* that the particular "form" or "X-ray" can be obtained/maintained in a "composition", the deficiency of description and enablement as compared to the *art standard* described in applicants' article *tricky business*, is self evident.

(10) Response to Argument

In response to **rejection (A)**, Appellants argued that:

> *it has long been the law that anticipation can properly be held only where a prior art document teaches each an every limitation of the rejected claim and inherency can not be established by probabilities or possibilities.*

It is the Examiner's position that:

A residue obtained, when (S)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-a-butyl}-aminocarbonylmethyl] benzoic acid in ethanol, was evaporated to remove solvent, is amorphous.

Two citations are hereby provided from the state of the art. The Berstein reference on p.254 clearly taught that "Amorphous pharmaceutical.....rapid solidification from the melt, lyophilization or spray drying, removal of solvents....." The Ronsen '612 reference taught that rotary evaporation as well as analogous spray drying will produce amorphous form which has essentially the same X-ray as the instant application figure 4 showing no peak in a powder X-ray diffraction.

It has been clearly explained in the rejection that "Any x-ray diffraction of an amorphous material is only to show no diffraction or non-crystalline. Therefore, the incorporation of x-ray diffraction into the base claim does not change the product or process, and anticipation is found."

Besides, it has been clearly explained to appellants that all "amorphous" forms are not polymorphic, and *is not a polymorph* as explicitly recited in the Ulicky physical chemical dictionary.

In response to **rejection (B)**, Appellants argued that:

"....prior art IR was obtained on racemic repaglinide in methylene solution..."

"...in the form of X-ray diffraction patterns disclosed in the instant specification, clearly demonstrating that the instant and prior art products are different"

It is the Examiner's position that:

The IR are identical:

The side by side comparison of the IR for the instant product and the prior art product was provided as EXHIBIT A.

Please note that the IR of the prior art was obtained from form A solid not in solution.

There are two products having identical infrared data, one is called repaglinide form III, another is repaglinide form A solid; thus, the two products are identical.

The state of the art reference by Baumann et al. is provided to show that it is conventional skill well known in the chemical art that IR differentiates stereoisomers and racemates (see the difference in IR of S, R and meso/racemic compounds). Therefore, when two products are merely different by private naming but displayed identical IR, they are the same product, i.e. anticipated.

X-ray demonstrating different product:

X-ray diffraction pattern can provide information on the crystalline nature of a compound, X-ray diffraction pattern **alone** does not demarcate the identity of two products.

It is well recognized in the crystalline solid art that

Sometimes the difference in X-ray diffraction is very minor and must be carefully evaluated before a definitive conclusion is reach [on whether there is true polymorphs] (US pharmacopia of record)

"...small changes in the powder X-ray patterns arise as artifacts rather than arising from polymorphism. We have found that many small changes in powder X-ray diffraction patterns are due to particle size/morphology or sample holder geometry" (Davidovich)

In addition, it is hereby provided two visual comparison from the text book by Berstein, the figure on p.272 showed that two identical X-ray pattern, but one is the chemical compound pigment Yellow 14, wherein R is CH3, while the other one is the pigment Yellow 63, R is Cl. Thus, identical X-ray displayed by **different compounds**. The figure on page 273 showed that two X-ray diffraction pattern collected on crystal and recrystal after melting. Although, there

are new peaks, the authors concluded that "it may not be a pure modification" i.e. not a true polymorph.

X-ray diffraction, is a useful tool, but the results must be used with caution and it is not an absolute determination of true polymorphs especially, in the instant application, the diffraction patterns are obtained in a powdered X-ray which are known to have many artifacts which mislead the result absent other verification of the chemical identity and nature of the product. (see Davidovich)

Especially, in the instant case, the IR spectrum showed such close similarity, Appellants provided no factual evidence other than that Appellants named the product differently and there is Powder X-ray diffraction pattern. It is immaterial how other compounds and their polymorphs may be identifiable by their X-ray diffraction, each product is unique and empirical in its own way. In the instant case, Appellants provided no rebuttal to the fact that the two IR spectra are identical; but only argued that they have different name and they have other data. Such "other" information provided no evidence as to why the IR spectra are the same; nor how the products were different.

In response to **rejection (C)**, Appellants argued:

> "*...there is no teaching or suggestion in the cited references that (S)-repaglinide exists in other polymorphic forms.....Appellants alone, disclose that crystalline form II of (S)-repaglinide can be prepared from a solvent containing an aromatic hydrocarbon but does not include petroleum ether*"

The Examiner's position is:

Appellants are unpersuasive as to the argument that the reference Grell et al. '924 did not suggest that repaglinide has polymorphic forms. Appellants' attention is drawn to col.32-33, example 11 wherein Form A, form B, Form C are made. Although the term "polymorph" was not used, one having ordinary skill in the art would have recognized that such transition of one form to another through melting and recrystallization; thus produced crystals which have lower and higher melting points are *polymorphic* crystals of the same compound.

Further, Appellants' attention is drawn to the fact that the claims are drawn to amorphous and polymorphic form III of repaglinide. Repaglinide form II was not under examination nor was the process of making form II in the claims. Please note that for the claimed invention, the amorphous form was made from alcoholic solvent systems (see claim 40); for form III, the solvent system is haloalkane (see claim 19). Nowhere in the claims is the issue of "aromatic hydrocarbon but not include petroleum ether" recited. Therefore, argument with respect to this limitation is unpersuasive.

Contrary to Appellants' argument, the recited Grell et al. reference employed alcoholic solvents as well as haloalkanes in various process of making the product for example: in example

1, col. 16, line 49, tetrachloride was used; in example 2 col. 20, line 33, chloroform was used; in example 3, col. 21, line 40, dichlorobenzene was used; in example 11, col. 32, line 48, ethanol was used. Therefore, both polymorphic forms, how to prepare them, and the different solvent systems are found through out the reference. The species of specific solvents rendered the claims of using haloalkane and alcoholic system prima facie obvious. Especially, the prior art using the variation of *effect oriented elements* produced a product with *identical IR*, thus, further provided evidence that such modification is conventional routine techneque to one having ordinary skill in the art and would be successful in obtaining the desirable products.

A state of the art reference from Wikipedia (encyclopedia over internet) further support the prima facie obvious nature of known pharmaceuticals having polymorphic forms because "*..every compound has different polymorphic forms, and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound*". In the instant case the very nature of repaglinide having polymorphic forms is disclosed in Grell '924, variations in process of making are disclosed in Grell '924, employing further variation flow naturally with the teaching of the prior art would proportionally increase the number of crystal forms, i.e. prima facie. In the instant case, the IR of form III is identical to the prior art form, in absence of careful comparative evaluation of single crystal X-ray, no clear factual evidence has been made of record that form III is not the same but only a variation of the prior art crystalline form A.

In response to **rejection (D)**, Appellants argued that:

> *"The subject matter of claims 8-18 is directed to a composition comprising crystalline form III.....that it is error to read such a limitation into the claims"*

It is the Examiner's position that:

The argument by Appellants is very confusing. If the composition comprising repaglinide form III does not intend to mean "a composition that the form be maintained", then what does it mean?

Preponderance of evidence in the state-of-the-art indicated that pharmaceutical compositions containing any particular crystalline form cannot be assumed but must be described and enabled with specificity and particularity. See for example:

> Muzaffar et al. p.60 "At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form ...." And p.63-65 (a)-(h) pharmaceutical preparing processes affect polymorphism;
>
> Jain et al. p.322-326, manufacturing processes that affect polymorphs ;

Doelker et al. Translation page 3, "more than half of the pharmaceutical compounds exhibit polymorphism.:....as such, they show at the solid state different physicalchemical properties which in turn may affect the technological and biopharmaceutical properties of active ingredients or excipients »

Translation page 34, "...crystalline state of the active principles, like that of the excipients, plays a *determining* role in the technological and biopharmaceutical characteristics of the solid or semi-solid phamaceutical forms. The pharmaceutical sceintist, like the chemist, therefore has the **requirement** to know as **completely** as possible the polymorphism.... »

Otsuke et al. p.852 « ...in formulation studies and the method preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic *phase transformation* of the bulk CBZ powder during the manufacturing process"

As observed in the enormous number of prior art that both the crystalline form of the active principle and what environment i.e. the process and excipients, it is in, must be completely known for one skilled in the art to practice such composition product.

Therefore, Appellants must first decide when the claims are drawn to "form III" does it mean it contains form III or not? A skilled person in the art would read the scope of claims 8-18 to *must contain form III*. This of course does not mean the active principle will exist indefinitely since all pharmaceutical products have a shelf life. On page 16 and 18 as recited by Appellants, the requirement of minimum amount of form III was described **without** any specific description of the environment i.e. excipients and processing parameters, that such form can be made into a composition. Such deficiency, as evidenced in the above state of the art teaching, provided insufficient description and enablement for the claims. Especially, there is no description as to under what circumstance the product will contain at least 80% i.e. a requirement to know as complete as possible.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons and factual evidence:

The multiple state-of-the-art references submitted are well known facts but provided for Appellants' convenience that patentability of a "product" must be evaluated case by case based on the conventional knowledge known for that product. In the instant case:

i) the claimed product does not have any difference in chemical identity i.e. compound vs hydrate of a compound, different in chemical identity;

ii) the claimed product has been known to have polymorphic forms and at least one physical characteristic, the IR, is identical;

iii) *powdered* X-ray alone does not decide on the novelty of a chemical product or novelty of a true morph;

iv) in absence of an operable composition with active principle, excipients and conditions of preparation clearly delineated, insufficient description was provided for the skilled artisan.

Therefore, the instant case is different from *Ex parte Havens, Ex parte Andrews or Ex parte Portmann*, because factual evidence indicated the natural flow of existence of new forms, obtaining new forms by spending time and money and new forms does not necessarily have any patentability advantage in either physical property (same IR) or formulation.

It is believed that the rejections should be sustained.

Respectfully submitted,

Celia Chang
Primary Examiner
Art Unit 1624

Conferees:

Christopher Low, tQUAS, TC 1600

CHRISTOPHER LOW
QUALITY ASSURANCE SPECIALIST
TECHNOLOGY CENTER 1600

Cecilia Tsang, Training SPE, TC1600

Cecilia J. Tsang
Supervisory Patent Examiner
Technology Center 1600

EXHIBIT A

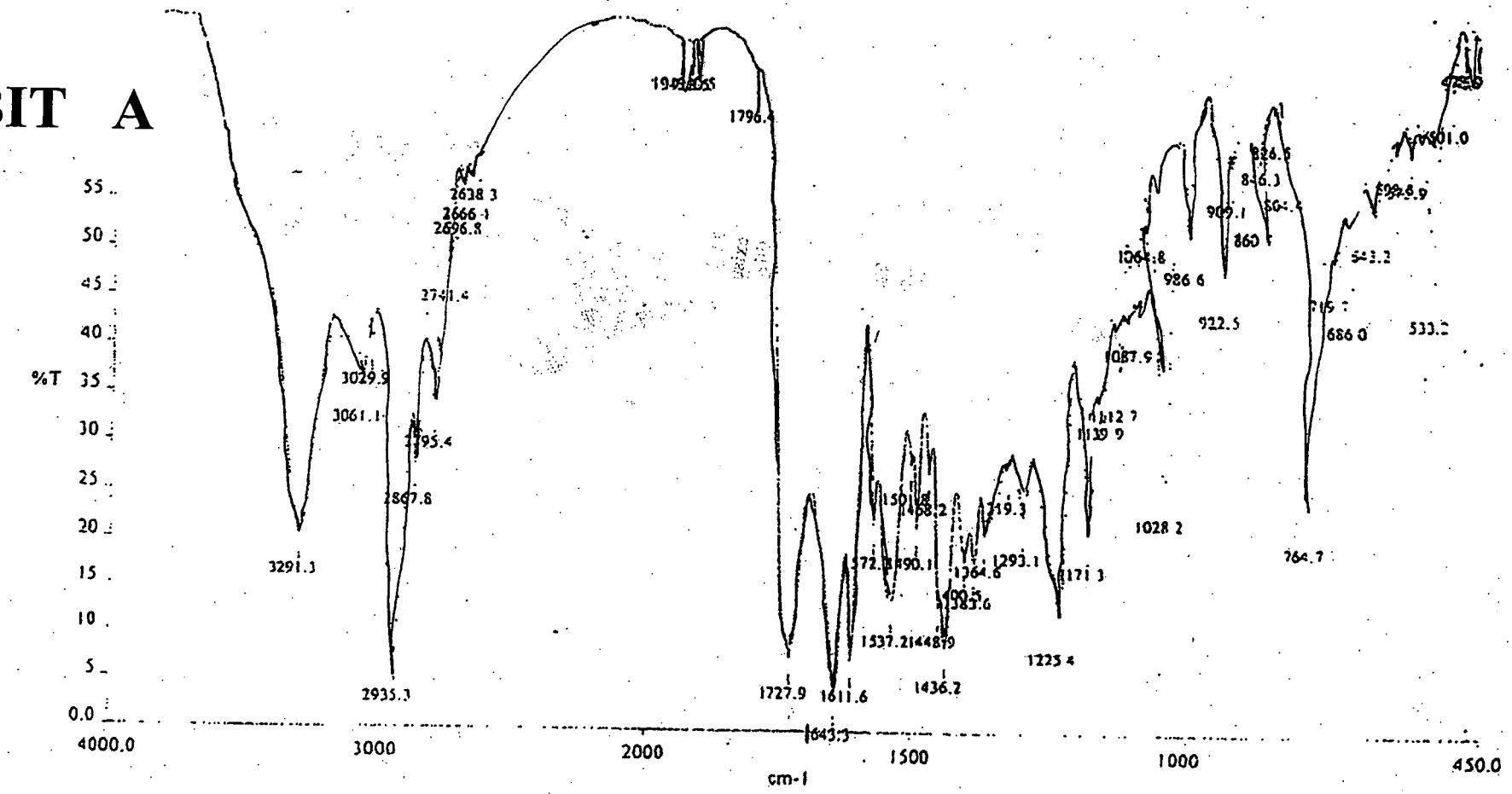


Fig. 4
(PART 1)

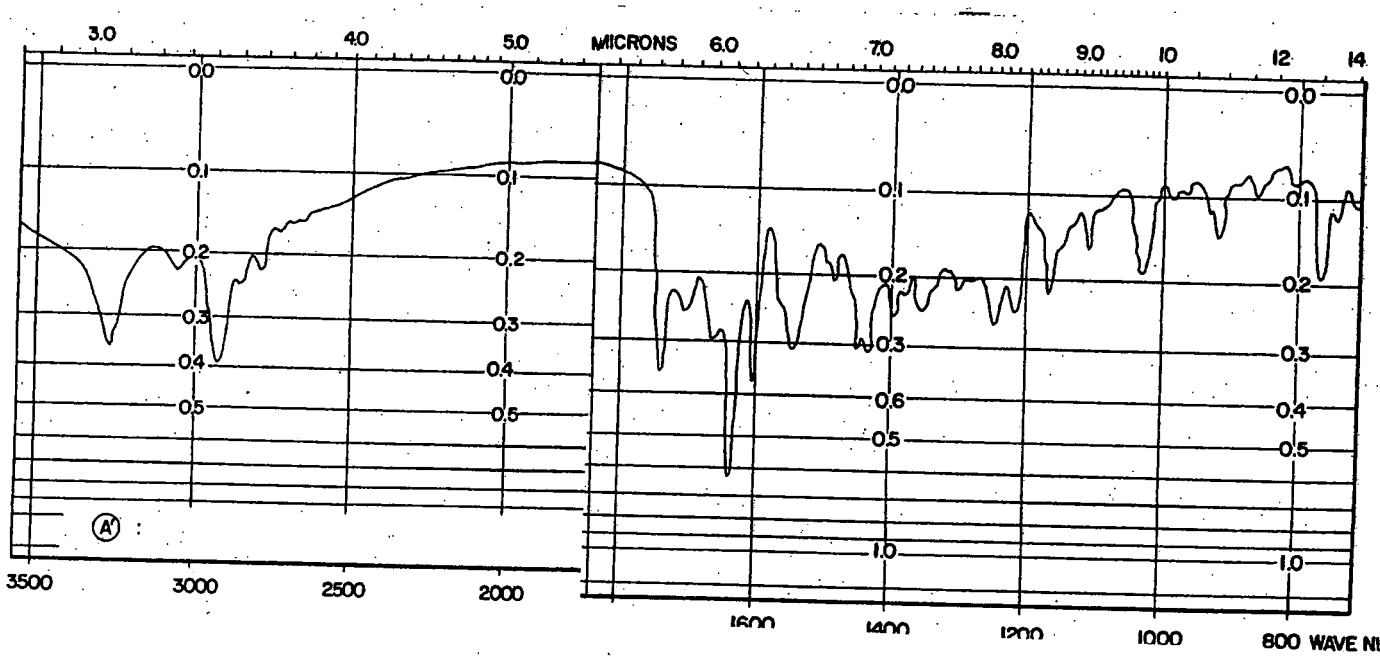


Fig. 4
(PART 2)

US005672612A

United States Patent [19]

Ronsen et al.

[11] Patent Number: 5,672,612

[45] Date of Patent: Sep. 30, 1997

[54] AMORPHOUS PAROXETINE COMPOSITION

[75] Inventors: Bruce Ronsen, River Forest; Ragab El-Rashidy, Deerfield, both of Ill.

[73] Assignee: Pentech Pharmaceuticals, Inc., Wheeling, Ill.

[21] Appl. No.: 708,802

[22] Filed: Sep. 9, 1996

[51] Int. Cl.[6] A61K 31/44

[52] U.S. Cl. 514/338; 546/197

[58] Field of Search 514/338; 546/197

[56] References Cited

U.S. PATENT DOCUMENTS

4,007,196	2/1977	Chistensen et al.	260/293.58
4,721,723	1/1988	Barnes et al.	514/321
5,151,448	9/1992	Crenshaw et al.	514/651
5,276,042	1/1994	Crenshaw et al.	514/321

Primary Examiner—Amelia Owens

Attorney, Agent, or Firm—Olson & Hierl, Ltd.

[57] ABSTRACT

A free-flowing, amorphous paroxetine hydrochloride-ethanol composition suitable as a therapeutic agent for premature ejaculation can be prepared by dissolving paroxetine free base in a hydrochloric acid-ethanol solution followed by drying. In a preferred embodiment, the amount of ethanol present in the amorphous product is in the range of 1 to 4 weight percent based on paroxetine hydrochloride. The amorphous product is stable and substantially non-hygroscopic.

11 Claims, 4 Drawing Sheets

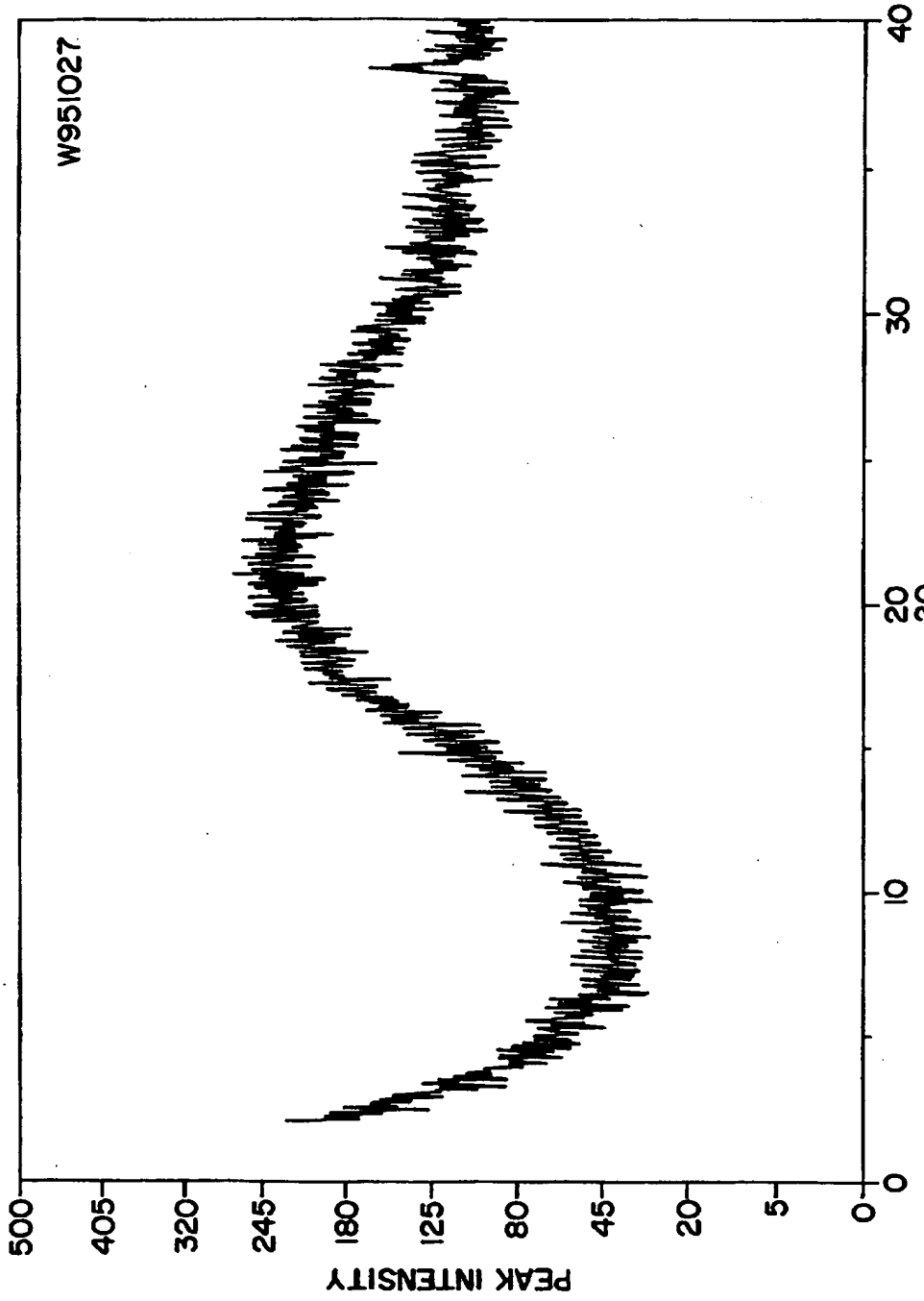

W951027
PEAK INTENSITY
500
405
320
245
180
125
80
45
20
5
0
0
10
20
30
40
2θ

FIG. 1

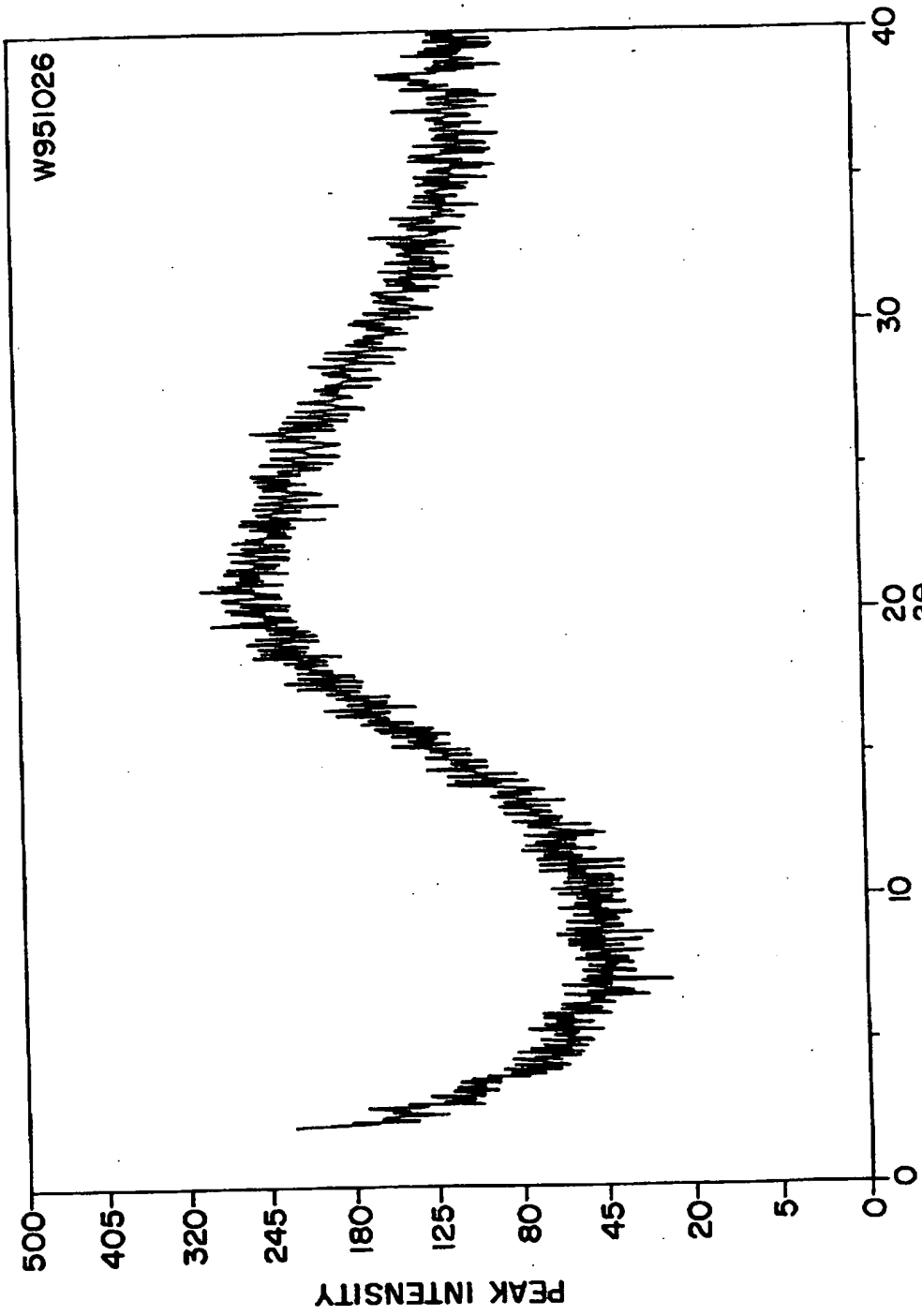

W951026
PEAK INTENSITY
500
405
320
245
180
125
80
45
20
5
0
0
10
20
30
40
2θ

FIG. 2

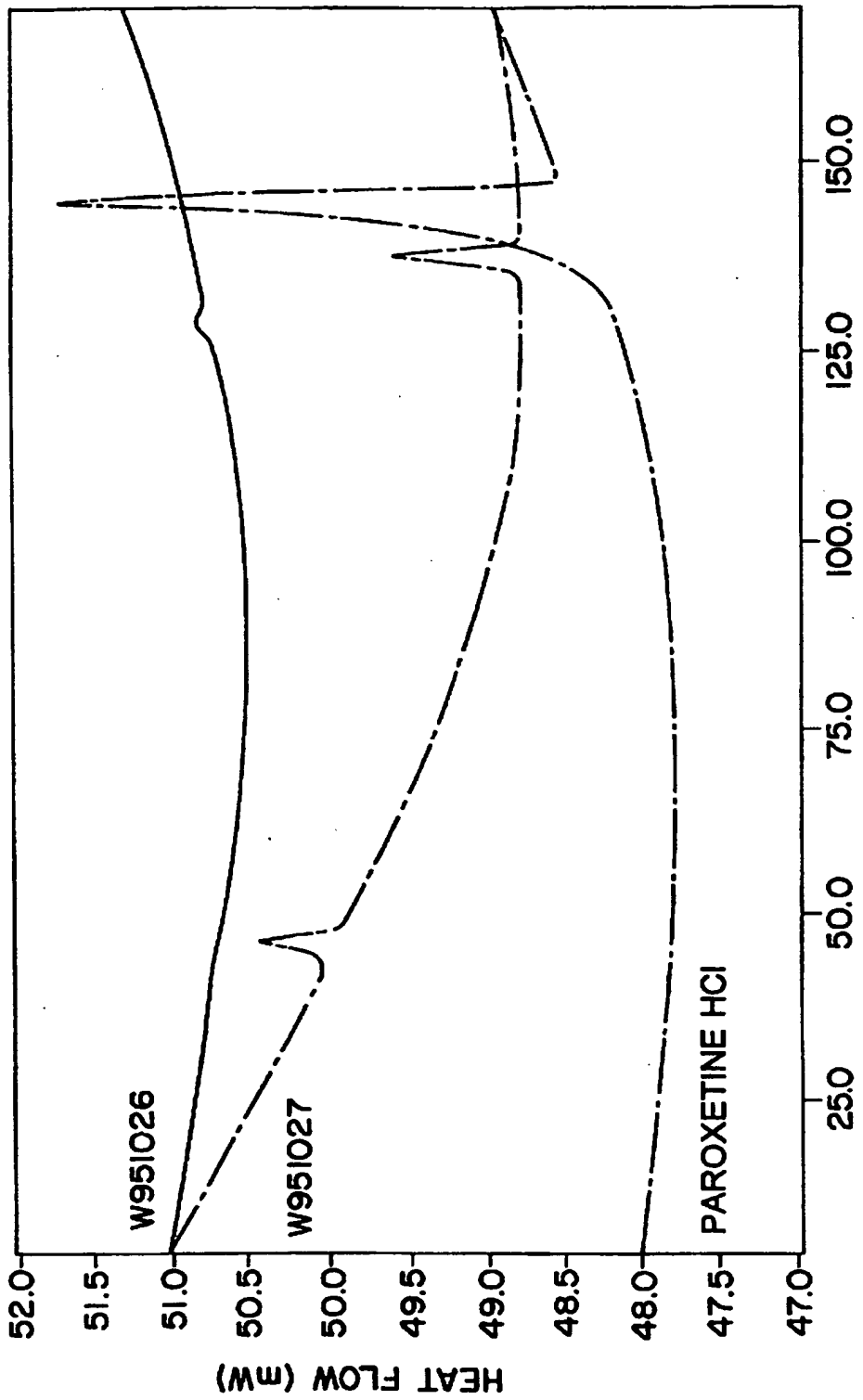

W951026
W951027
PAROXETINE HCl
HEAT FLOW (mW)
52.0
51.5
51.0
50.5
50.0
49.5
49.0
48.5
48.0
47.5
47.0
25.0
50.0
75.0
100.0
125.0
150.0
TEMPERATURE (°C)
RATE I: 5.0 C/min

FIG. 3A

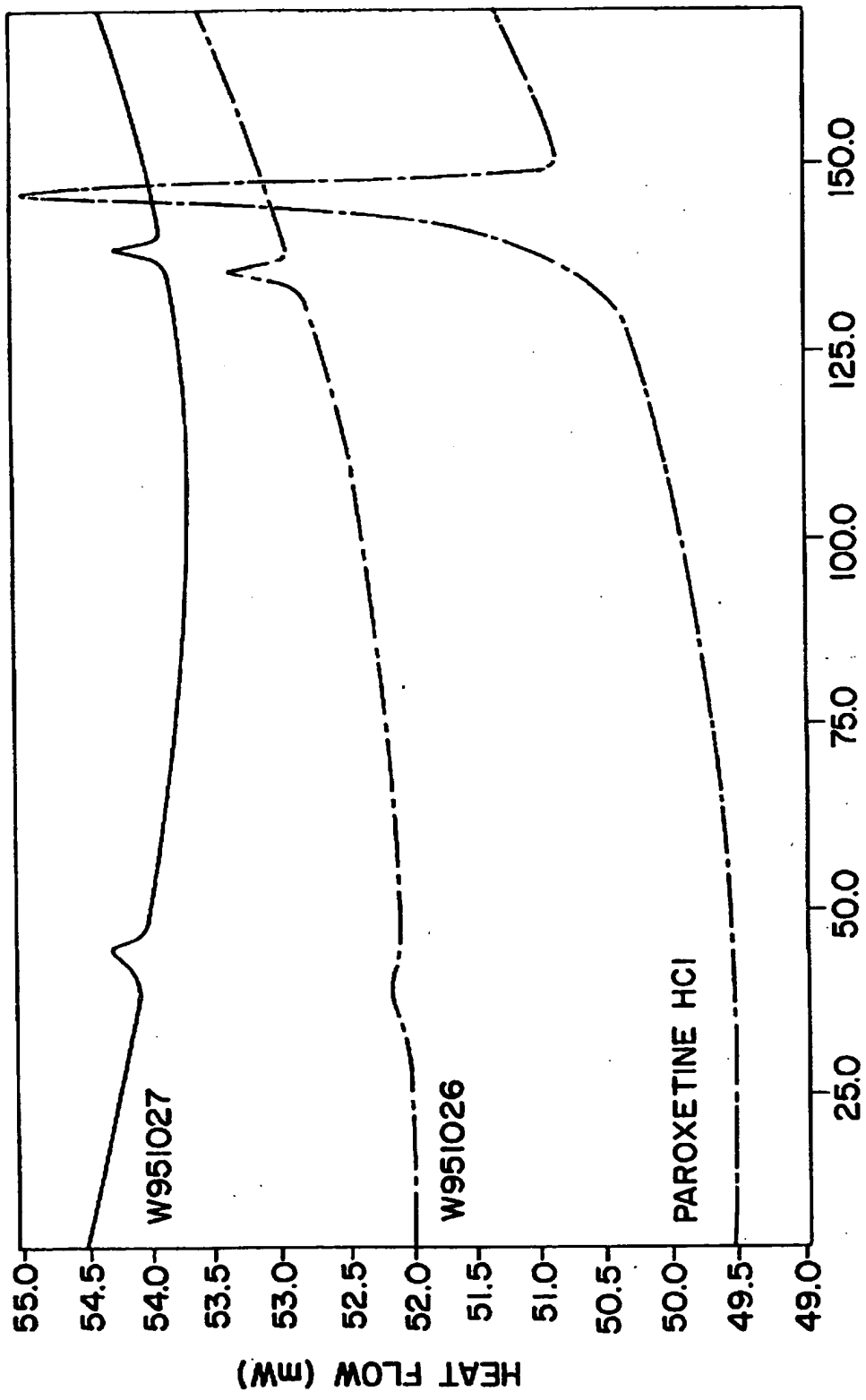

W951027
W951026
PAROXETINE HCl
RATE 1: 10.0 C/min
TEMPERATURE (°C)
25.0
50.0
75.0
100.0
125.0
150.0
HEAT FLOW (mW)
55.0
54.5
54.0
53.5
53.0
52.5
52.0
51.5
51.0
50.5
50.0
49.5
49.0

FIG. 3B

AMORPHOUS PAROXETINE COMPOSITION

FIELD OF THE INVENTION

This invention relates to an amorphous paroxetine composition suitable as a therapeutic agent for sexual dysfunction and to a process for preparing such composition.

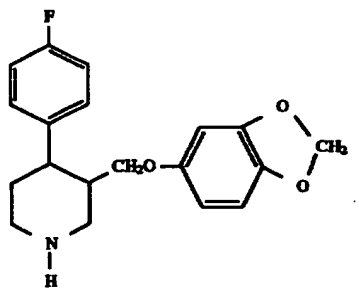
BACKGROUND OF THE INVENTION

The selective serotonin reuptake inhibitor (SSRI) antidepressants have recently emerged as effective new treatments for patients with premature ejaculation. In general, antidepressants influence more than one neurotransmitter system and have affinity for multiple receptors. This heterogeneity of action produces mixed effects, including those on the sexual response cycle. Sexual dysfunction associated with antidepressants, including delayed and completely abolished ejaculation, has been a subject of numerous case reports, studies, and review articles [for example, *J. Clin. Psychiatry* 54, 209–212, (1993); *J. Clin. Psychopharmacol.* 3, 76–79, (1983); *J. Clin. Psychiatry* Mon. 10, 4–10, (1992); *Depression* 2, 233–240, (1994/1995)]. Because of the lack of abuse potential, relatively benign side effect profile, and fairly consistent reports of delayed ejaculation, SSRI antidepressants seem to be a safe treatment option for patients with premature ejaculation, especially in cases of failed psychological treatment.

The use of the SSRI antidepressant fluoxetine hydrochloride (Prozac®) in this regard has been described in U.S. Pat. No. 5,151,448 to Crenshaw et al. A similar treatment, at a relatively lower dosage of active ingredient, has been described in U.S. Pat. No. 5,276,042 to Crenshaw et al. for the SSRI antidepressant paroxetine hydrochloride (Paxil®). Other anti-anxiety drugs such as chlordiazepoxide (Librium®) and diazepam (Valium®) are not suitable for the treatment of premature ejaculation.

The preparation of a class of SSRI antidepressants has been disclosed in U.S. Pat. No. 4,007,196 to Christensen et al. In Example 2 of this patent, the preparation of (−)-trans-4R-(4'-fluorophenyl)-3S-[(3'4'-methylenedioxy-phenoxy) methyl]-piperidine (generic name paroxetine) is described (formula A),

(A)



wherein paroxetine is obtained as a free base then converted to its maleic acid salt. The use of the acetate salt of paroxetine has been described [*Psychopharmacology* 57, 151–153 (1978); *Psychopharmacology* 68, 229–233 (1980); *European Journal of Pharmacology* 47, 351–358 (1978)]. There also has been limited use of the hydrochloride salt in aqueous solution [*Acta. Pharmacol. et Toxicol.* 44, 289–295 (1979)]. More recently, U.S. Pat. No. 4,721,723 to Barnes et al. has disclosed the preparation of a crystalline paroxetine hydrochloride hemihydrate. However, this particular process requires post-synthetic treatment of the product in order to obtain the crystalline adds to the difficulty and overall cost of production. Amorphous paroxetine hydrochloride has been reported by Barnes et al. to be undesirably hygroscopic.

The present invention provides an economical manufacturing process for the preparation of a substantially non-hygroscopic, free-flowing, amorphous paroxetine hydrochloride-ethanol composition suitable as a therapeutic agent for the treatment of premature ejaculation.

SUMMARY OF THE INVENTION

Amorphous paroxetine hydrochloride-ethanol composition and method for its production are disclosed. The present inventive method generates amorphous, substantially non-hygroscopic paroxetine hydrochloride from a reaction of paroxetine base with a hydrochloric acid/ethanol solution followed by drying of the product. This invention overcomes inherent problems associated with crystallization methods of the prior art, including the recovery of product.

The paroxetine base can be prepared according to the procedure set forth in U.S. Pat. No. 4,007,196 to Christensen et al. Paroxetine hydrochloride solute is obtained by combining an appropriate amount of hydrochloric acid in absolute ethanol with the free base. The amorphous composition is produced upon drying of the product. In a preferred embodiment, the amount of ethanol present in the product is not more than about 10 percent by weight based on the paroxetine hydrochloride. Under this condition, the amorphous composition is a substantially non-hygroscopic solid, thus providing a manufacturing advantage. In a more preferred embodiment, the amount of ethanol present in the composition is in the range of about 1 to about 4 weight percent, based on paroxetine hydrochloride. This amorphous composition is stable and is amenable to incorporation into both tablet and suppository dosage forms.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings,

FIG. 1 is the diffraction pattern of the amorphous paroxetine composition, lot #W951027. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

FIG. 2 is the diffraction pattern of the amorphous paroxetine composition, lot g W951026. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

FIG. 3A illustrates the results of differential scanning calorimetry done at a heating rate of 5° C./minute on the reference sample paroxetine hydrochloride and two amorphous samples, lot #'s W951027 and W951026. The horizontal axis represents temperature (°C.) and the vertical axis corresponds to the heat flow (mW).

FIG. 3B illustrates the results of differential scanning calorimetry done at a heating rate of 10° C./minute on the reference sample paroxetine hydrochloride and two amorphous samples, lot #'s W951027 and W951026. The horizontal axis represents temperature (°C.) and the vertical axis corresponds to the heat flow (mW).

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

A free-flowing, substantially non-hygroscopic solid form of paroxetine hydrochloride-ethanol is obtained by combining paroxetine base with a hydrochloric acid/ethanol solution and drying of the product. The drying step can be effected by spray-drying, vacuum drying and the like.

The paroxetine base can be obtained according to the procedure of U.S. Pat. No. 4,007,196 to Christensen et al.

Absolute ethanol is added in an amount sufficient to dissolve the paroxetine base, the molar ratio of paroxetine base to absolute ethanol preferably being in the range of about 10% v/v to about 15 % w/v. A solution of hydrochloric acid in absolute ethanol preferably in the range of about 10% v/v to about 30% v/v, usually about 22% v/v, is added to the paroxetine base solution and stirred at ambient temperature and pressure for a time period sufficient to produce paroxetine hydrochloride salt. The preferred molar ratio of paroxetine base to hydrochloric acid is in the range of about 1:1 to about 1:10. The reaction temperature is preferably in the range of about 15° C. to about 40° C. along with a preferred reaction time in the range of about 10 minutes to about 40 minutes. The resulting solution was then dried by rotary evaporation or spray drying to obtain the desired amorphous paroxetine hydrochloride-ethanol composition. The drying time preferably ranges from about 8 hours to about 72 hours. The amount of ethanol present in the final product relative to paroxetine hydrochloride is not more than about 10 weight percent, more preferably in the range of about 1 to about 4 weight percent.

Example 1

Preparation of Amorphous Paroxetine HCl-Ethanol Composition: Vacuum Drying Method

To a reaction flask containing 100 ml of absolute ethanol was added to 13.9 g of paroxetine base. The flask was shaken until a clear solution was obtained. To this paroxetine solution, 10 ml of a solution of hydrochloric acid in absolute ethanol (22% v/v) was added dropwise. As the reaction proceeded to completion, the color of the solution changed from a yellow brown to a pink brown. The product was then vacuum dried in a rotary evaporator. A foamy, amorphous solid was obtained (lot #W951027). The produced amorphous solid was subjected to an additional 2.5 days of drying in a dessicator at reduced pressure. The solid, a free-flowing powder, was tested for composition by NMR and FTIR. The findings were consistent with published spectra for paroxetine. Silver nitrate testing of the solid indicated the presence of chloride in the sample. Volatile analysis by gas chromatography revealed that the amount of ethanol present in the amorphous solid was 4% by weight. Residual moisture was determined by Karl-Fisher coulometric method at 0.7%. HPLC analysis revealed the material was >99% pure and essentially free from contamination. X-ray powder crystallography was conducted on the sample and produced the diffraction pattern shown in FIG. 1. X-ray powder diffraction was performed using the powder pack method. The powder patterns were obtained using a Philips PW1710 automated diffractometer, with monochromatized CuK_α ($K_{\alpha1}$=1.54060 Å; $K_{\alpha2}$=1.54438 Å) radiation. The diffractometer was equipped with a compensating slit and a graphite monochromator. It was calibrated to 0.02° (2θ) using the quartz peak at 26.66° (2θ). The minimum peak/background ratio was 0.75. This spectrum is consistent with an amorphous solid form. The halo effect is clearly seen and the intensity is small. Differential scanning calorimetry was performed on the solid at two different heating rates. The results indicate an endotherm at 48° C. (heat flow) with and absence of other endotherms (FIG. 3A and FIG. 3B). Visual examination showed a "glassing" of the solid at this temperature.

A specimen (0.5 g) was stored in a glass container with a HDPE liner for stability testing. The container was opened and closed periodically exposing the specimen to atmospheric moisture. Moisture determination was conducted at intervals of about 3 months. Appearance of the material was noted, summarized in TABLE 1, below.

TABLE 1

Stability of Paroxetine-HCl/ethanol, amorphous, lot #W951027

TIME	Initial	3 months	6 months
APPEARANCE	Free-flowing powder	Free-flowing powder	Free-flowing powder
MOISTURE	0.7% w/w	1.8% w/w	2.1% w/w

EXAMPLE 2

Preparation of Amorphous Paroxetine-HCl/Ethanol Composition: Spray Drying Method

A solution of paroxetine hydrochloride in absolute ethanol (3.2 g/100 ml) was prepared as described in EXAMPLE 1. The solution was charged into a spray-drying machine (Yamato Chemical Co.) using a standard nozzle (0.1 mm orifice). The inlet temperature was set at 90° C. and the outlet temperature at 60° C. The sample was spray dried to a fine, off-white powder (lot #W951026). Following recovery, the material was transferred to a vacuum dessicator and dried under partial vacuum for an additional 2.5 days. The resulting solid, a free-flowing powder, was tested for composition by NMR and FTIR. The findings were consistent with published spectra for paroxetine. Silver nitrate solution addition to an aqueous solution of the powder produced a white precipitate indicative of chloride. Volatile analysis by gas chromatography revealed that the amount of ethanol residual was about 0.3% w/w. Residual moisture in the product was 0.8% measured by Karl-Fisher coulometric method. A sample was analyzed by HPLC and found to be free from related substances (purity >99%). X-ray powder crystallography was conducted producing the diffraction pattern shown in FIG. 2. This spectrum is consistent with an amorphous form. Differential scanning calorimetry was conducted on the solid. The results showed an endotherm at 48° C. (see FIG. 3A and FIG. 3B). Visual examination of the sample showed a "glassing" of the solid at this temperature.

For stability testing a specimen (9 g) was stored in a glass container with a HDPE liner. The container was opened and closed periodically exposing the specimen to atmospheric moisture. Moisture determination was conducted at intervals of about 3 months. Appearance of the material was noted with the findings summarized in TABLE 2, below.

TABLE 2

Stability of Paroxetine HCl/ethanol, amorphous, lot #W951026

TIME	Initial	3 months	6 months
APPEARANCE	Free-flowing powder	Free-flowing powder	Free-flowing powder
MOISTURE	0.8% w/w	2.1% w/w	2.2% w/w

The foregoing is intended to be illustrative of the present invention, but not limiting. Numerous variations and modifications of the present invention may be effected without departing from the true spirit and scope of the invention.

We claim:

1. A solid, stabilized amorphous paroxetine hydrochloride composition which comprises paroxetine hydrochloride and ethanol; the ethanol being present in the composition in an amount not more than about 10 percent by weight, based on said paroxetine hydrochloride.

2. The composition in accordance with claim 1 wherein said ethanol is present in an amount in the range of about 1 to about 4 weight percent, based on said paroxetine hydrochloride.

3. The composition in accordance with claim 1 and in tablet form.

4. The composition in accordance with claim 1 and in suppository form.

5. A process for the production of an amorphous paroxetine hydrochloride-ethanol composition comprising:

(a) dissolving paroxetine free base in absolute ethanol;

(b) adding a solution of hydrochloric acid in absolute ethanol to the paroxetine base solution;

(c) stirring the resulting solution for a period of time sufficient to produce a composition of paroxetine hydrochloride in ethanol; and

(d) drying the paroxetine hydrochloride-ethanol composition.

6. The method of claim 5 wherein the reaction temperature is in the range of about 15° C. to 40° C.

7. The method of claim 5 wherein the ratio of paroxetine base to absolute ethanol is in the range of about 10% w/v to about 15% w/v.

8. The method of claim 5 wherein the molar ratio of paroxetine base to hydrochloric acid is in the range of about 1:1 to about 1:10.

9. The method of claim 5 wherein the ratio of hydrochloric acid to ethanol is in the range of about 10% v/v to about 30% v/v.

10. The method of claim 5 wherein the reaction time is in the range of about 10 minutes to about 40 minutes.

11. The method of claim 5 wherein the drying time is in the range of about 8 hours to about 72 hours.

* * * * *